

Epidemiology, Prenatal Diagnosis, and Neonatal Outcomes of Congenital Heart Defects in Eastern China: A Hospital-Based Multicenter Study

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Research article

Keywords: Congenital heart disease, epidemiology, prenatal detection, neonatal outcome

Posted Date: April 29th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-24867/v1>

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Version of Record: A version of this preprint was published on September 2nd, 2020. See the published version at <https://doi.org/10.1186/s12887-020-02313-4>.

Abstract

Background : Congenital heart disease (CHD) is one of the most common birth defect. Currently, the reported occurrence of CHD continues to increase at global or regional level. In 2013, Chinese government announced to end 1-child birth policy. We aimed to update the incidence, prenatal diagnosis, and neonatal outcomes of CHD since the ending of 1-child policy, in eastern China.

Study design : Data were obtained from the Zhejiang provincial birth defects surveillance system. CHD identified during 2014-2018 were analyzed. Chi-square test, odds ratio (OR) and 95% confidence interval (CI) were used to explore incidence trends, prenatal diagnosis, birth outcomes and associated risk factors with CHD.

Results : Overall, 8,546 of 534,002 births were identified with CHD. During the period, the overall incidence of CHD increased significantly, giving an average incidence as 16.0 per 1000 births (95% CI 15.69-16.32). However, the incidence of critical CHD (CCHD) remained stable over time (1.6 per 1000 births, 95% CI 1.47-1.69). Women aged less than 20 years (OR 2.1, 95% CI 1.9-2.3) or ≥ 35 years (OR 1.2, 95% CI 1.2-1.3) were at higher risk of CHD than women aged 21-34 years. Births in urban areas (OR 1.2, 95% CI 1.2-1.3), male sex (OR 1.3, 95% CI 1.3-1.4), and multiple births (OR 4.0, 95% CI 3.7-4.4) had a higher risk of CHD than births in rural areas, female sex, and singletons, respectively. The three major subtypes of CHD were atrial septal defect (ASD, 68.0%), patent ductus arteriosus (PDA, 34.7%), and ventricular septal defect (VSD, 6.4%). A total of 22.2% of CHD was detected prenatally. Regarding to perinatal outcomes, there were 1457 (17.1%) stillbirths, 106 (1.2%) early neonatal deaths, and 6983 (81.7%) live births.

Conclusion : The high incidence of CHD might be attributable to the large proportion of mild CHD. Pregnancies in urban areas, male births, and younger or older women were the risk factors for CHD. The prenatal detection rate for overall CHD was low, whereas the rate for CCHD was similar or even higher than other studies. The neonatal outcomes were comparable to previous literatures.

Background

Congenital heart disease (CHD) is the most prevalent congenital malformation. The cause of CHD is multi-factorial, such as genetic defects, role of environmental agents, interaction of genetic and environmental factors or even some unknown reasons [1, 2]. The global average prevalence of CHD at birth was 9.4 per 1000 live births during 2010–2017, which varied with geographical regions and CHD categories [3]. To best our knowledge, atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), tetralogy of Fallot (TOF) were the most common subtypes of CHD [3–5].

CHD is the main cause of fetal and infant death. Indeed, disparities in CHD mortality is related to CHD subtypes, maternal race and pediatric cardiac development et al. The 1-year infant mortality rate from CHD ranges from 0.33‰ to 2‰, which is worse in critical CHD (CCHD) and those prenatally diagnosed [6–9]. Even patients living with CHD are strongly associated with other complications, such as heart

failure, lung infection, and endocarditis, which affect the patient's physical and mental health to some degree [10–12]. For infants with CCHD, they frequently require medical care or surgical intervention [1, 13].

China is facing a great burden of CHD for its huge population, where the prevalence of CHD vary from 7.6 to 22.9 per 1000 live births or perinatal infants in previous researches [14–19]. Studies on the epidemiology of CHD in China usually focus on births at and over 28 gestational weeks, and to fully understand the occurrence of CCHD is limited. Recently, the Chinese government has announced a birth policy adjustment from the 1-child policy to a universal 2-child policy [20]. Throughout the period of birth policy adjustment, we noticed significant changes of childbearing women and the strengthen of congenital anomalies prevention. However, CHD has remained as the leading malformation with increasing trend [21]. Zhejiang Province is located in eastern China and total population is approximately 57 million [22]. Of this province, maternal and child health is at the leading level in China [23]. Provincial hospital-based birth defect surveillance has been conducted in Zhejiang for over than 30 years. The surveillance system includes 90 hospitals in 30 regions. In this study, we comprehensively investigated the incidence, prenatal diagnose, subtypes and early neonatal outcomes of CHD in Zhejiang Province over the period of birth policy changes. Our findings will be beneficial for preventing and intervening CHD since the end of the 1-child policy in China.

Methods

Study population

A hospital-based birth defects surveillance system in Zhejiang Province accounts for one third of the total births in this province annually. The registry system captures congenital anomalies in all births, including early fetal loss (death < 28 gestational weeks), stillbirth (fetal death at or over 28 gestational weeks), live birth, and early neonatal death (death \leq 7 days after birth). Singleton and multiple births are recorded. We retrospectively collected data of CHD that was reported during 2014–2018 in the registry system.

A questionnaire was used for data collection by medical staff in surveillance hospitals. Information on the characteristics of childbearing women and their births, CHD diagnosis, subtypes of CHD, and perinatal outcomes, was collected from clinical records or mother and child health care books. Quality control was performed from community hospitals to provincial hospitals. The study was approved by the Medical Ethical Committee of Women's Hospital, School of Medicine, Zhejiang University.

Antenatal care and CHD diagnose

In China, maternal health services as part of the basic public health services have been implemented for over ten years. Pregnancy women routinely receive their first antenatal care (ANC) before 13 gestational weeks in Zhejiang province. Following this, they are suggested to use at least five times of ANC before delivery. More ANC visits for women with high risks are recommended, such as those aged \geq 35 years, with previous adverse pregnancy outcomes and those with abnormal findings in the current pregnancy.

For prenatal CHD screening, if the fetal nuchal translucency thickness was over 2.5 mm at a scan during 13 weeks or there was a high risk for chromosomal abnormality by serological screening, pregnant women were recommended to have echocardiography at 16 to 18 gestational weeks for the possibility of CHD. For most normal pregnant women, the echocardiography scans were conducted between 24 and 28 weeks' gestation, regardless of the findings during their first trimester screening.

For postnatal CHD screening, neonates with positive prenatal echocardiography or abnormal heart auscultation were suggested to have CHD screening during 2014–2017. Since 2018, all neonates received pulse oximetry monitoring (by trained nurses) combined with heart auscultation (by pediatricians) in the first 48 to 72 hours after birth. Those with positive records of prenatal echocardiography or with abnormal findings in CHD screening were required to have neonatal ultrasound screening for CHD. The final diagnosis was based on neonatal echocardiographic and clinic findings that were performed by an ultrasound doctor and pediatricians. Some patients with CHD had the diagnosis confirmed by a cardiologist through surgery or autopsy.

In this study, the diagnosis of CHD was coded using the International Classification of Diseases version 10 (ICD-10) and subtypes were classified by the codes Q20 to Q26. We excluded isolated patent foramen ovale and isolated PDA in preterm birth, PDA (< 3 mm in diameter). We included all ASD regardless of diameter. In this study, we defined 12 types of CHD as CCHD: persistent truncus arteriosus (PTA), double-outlet right ventricle, transposition of the great vessels, single ventricle (SV), TOF, pulmonary valve atresia, hypoplastic right heart (HRH), aortic valve stenosis (AoS), hypoplastic left heart syndrome (HLHS), coarctation of the aorta (COA), interrupted aortic arch (IAA), and total anomalous pulmonary venousreturn (TAPVR).

Analysis

Data were electronically registered. SPSS 25.0 (IBM Corp, Armonk, New York) was used for data analysis. The incidence of CHD was presented as the number of CHD per 1000 births (including both stillbirths and live births). Continuous variables were presented as mean and standard deviation (SD), and categorical variables as number and percentage. Chi-square trend analysis was used to track changes in the incidence of CHD over time. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to examine the risk factors for CHD. *P* values < 0.05 were considered statistically significant.

Results

Patients' characteristics and risk factors for CHD

During the study period, 8,546 of 534,002 births were identified with CHD, giving an average incidence of CHD as 16.0 per 1000 births (95% CI 15.69–16.32). The mean age of childbearing women was 28.9 ± 5.1 years (range: 15–50 years). Women with younger (OR 2.11, 95%CI 1.88–2.31) or advanced age (OR 1.25, 95%CI 1.18–1.33) were at higher risk of CHD than those aged 21–34 years (both *P* < 0.001).

Additionally, births in urban areas (OR 1.24, 95% CI 1.18–1.31), male sex (OR1.34,95%CI 1.28–1.40), and multiple births (OR4.03, 95%CI 3.70–4.40) were associated with increased risks of CHD compared with births in rural areas, female sex, and singletons (all $P < 0.001$, Table 1).

Table 1
Patients' characteristics and risk factors for CHD

Variable		Births (n)	CHD (n)	Incidence (per 1000 births)	OR value and 95% CI	P value
Maternal age (years)	< 20	9,879	312	31.8	2.11(1.88–2.31)	< 0.001
	21–34	456,027	6,944	15.3	Ref	
	≥ 35	68,096	1,290	18.9	1.25(1.18–1.33)	< 0.001
Area	Urban	320,029	6,343	19.8	1.24(1.18–1.31)	< 0.001
	Rural	138,754	2,203	15.9	Ref	
Birth gender	Male	253,015	4,614	18.2	1.34(1.28–1.40)	< 0.001
	Female	280,921	3,843	13.7	Ref	
	Unknown	-	65	-	-	-
Singleton		524,108	7,965	15.2	Ref	
Multiple birth		9,894	581	58.7	4.03(3.70–4.40)	< 0.001

Trends in CHD incidence and categories

The overall incidence of CHD increased greatly from 12.7 per 1000 births in 2014 to 20.6 per 1000 births in 2018, rising by 41.3% ($\chi^2_{trend} = 181.41$, $P < 0.001$). Of them, 842 were CCHD, accounting for 9.9% of total CHD, and resulting in an average incidence of 1.6 per 1000 births (95% CI 1.47–1.69). During the study period, the incidence of CCHD remained stable ($\chi^2 = 0.26$, $P = 0.609$, Table 2). The most frequent subtype of CHD was ASD (68.0%, 10.9 per 1000 births), and was followed up by PDA (34.7%, 5.5 per 1000 births), and VSD (16.4%, 2.6 per 1000 births). From 2014–2018, the incidences of ASD ($\chi^2_{trend} = 86.47$, $P < 0.001$), PDA ($\chi^2_{trend} = 165.23$, $P < 0.001$) and VSD ($\chi^2_{trend} = 13.00$, $P < 0.001$) increased by 58.4%, 102.5% and 45.0%, respectively (Fig. 1). The proportion of associated anomalies was 13.7% (1167/8546) in total CHD, whereas it was 29.1% (245/842) in CCHD.

Table 2
Trends in the incidence of CHD and CCHD during 2014–2018 (per 1000 births)

Time	Birth(n)	Critical CHD		Total CHD	
		N	Incidence(‰)	N	Incidence (‰)
2014	107,639	164	1.5	1363	12.7
2015	91,423	171	1.9	1496	16.4
2016	119,976	188	1.6	1670	13.9
2017	114,545	146	1.3	1951	17.0
2018	100,419	173	1.7	2066	20.6
total	534,002	842	1.6	8546	16.0
χ^2		0.26		181.41*	
<i>P</i>		0.609		< 0.001	
*: time trend					

Table 3
Rank of subtypes of CHD by incidence

Rank	Subgroup	N	Incidence Per 1000 birth	Proportion (%)
1	ASD/Q21.1	5807	10.9	67.9
2	PDA/Q25.0	2963	5.5	34.7
3	VSD/Q21.0	1398	2.6	16.4
4	AVSD/Q21.2	368	0.7	4.3
5	TOF/Q21.3	269	0.5	3.1
6	IAA/Q25.4	131	0.2	1.5
7	Pulmonary stenosis/Q25.6	113	0.2	1.3
8	Double outlet right ventricle/Q20.1	108	0.2	1.3
9	SV/ Q20.4	88	0.2	1.0
10	Transposition of great vessels/Q20.3	90	0.2	1.1
11	Hypoplastic left heart syndrome / Q23.4	65	0.1	0.8
12	COA/Q25.3	64	0.1	0.7
13	PTA/ Q20.0	68	0.1	0.8
14	Dextrocardia/Q24.0	61	0.1	0.7
15	HRH/ Q22.6	40	0.1	0.5
16	Pulmonaryvalve atresia/Q22.0	27	0.1	0.3
17	AoS/Q23.0	9	< 0.1	0.1
18	TAPVR/Q26.2	8	< 0.1	0.1

Table 4
Rank of prenatal detection subgroups of CHD

Rank	Subgroup	Prenatal detection	Proportion (%)
1	SV/ Q20.4	87	98.9
2	Hypoplastic left heart syndrome/ Q23.4	64	98.5
3	Double outlet right ventricle/Q20.1	105	97.2
4	PTA/ Q20.0	64	94.1
5	HRH/ Q22.6	37	92.5
6	TOF/Q21.3	245	91.1
7	COA/Q25.3	58	90.6
8	Pulmonary stenosis/Q25.6	101	89.4
9	AoS/Q23.0	8	88.9
10	Dextrocardia/Q24.0	53	86.9
11	Pulmonary valve atresia/Q22.0	23	85.2
12	IAA/Q25.4	112	85.5
13	Transposition of great vessels/Q20.3	72	80.0
14	TAPVR/Q26.2	5	62.5
15	AVSD/Q21.2	205	55.7
16	VSD/Q21.0	649	46.4
17	PDA/Q25.0	121	4.1
18	ASD/Q21.1	206	3.5

Prenatal detection and outcomes of CHD

A total of 22.8% (1949/8546) CHD were prenatally detected at a mean gestational age of 25.7 ± 5.2 weeks. The prenatal detection rate was higher in CCHD (90.0%, 758/842) than in total CHD ($\chi^2 = 1687.67$, $P < 0.001$). SV, hypoplastic left heart syndrome, and double-outlet right ventricle appeared in the top three ranks by prenatal detection rate. Of CHD diagnosed during pregnancy, 1.2% (23) of them were detected in the first trimester, 72.8% (1420) in the second trimester and 26.0% (506) in the third trimester, respectively. With regard to perinatal outcomes of CHD, the proportion of stillbirth was 17.1% (1457), that for early

neonatal death was 1.2% (106), and that for live birth was 81.7% (6983). For prenatally diagnosed pregnancies, 74.7% terminated (1456/1949).

Discussion

This multicenter study covers 534,002 births in 90 surveillance hospitals throughout the period of birth policy changes (2014–2018) in China. The large sample size could accurately access epidemiology of CHD since the ending of 1-child policy, regardless of common or rare subtypes of CHD. We noticed the potential risks of CHD were younger (< 20 years) and older (≥ 35 years) maternal age, births in urban areas, male sex, and multiple births. Despite overall incidence of CHD increased considerably over the entire study period, CCHD incidence were stable and neonatal outcomes of CHD were comparable. ASD, PDA and VSD were predominant subtypes of CHD with progressive increases. The prenatal detection rate of CHD differed with categories, whereas it was higher in CCHD or CHD with one more malformations.

It has been widely reported that CHD increased with maternal age [15, 16, 24]. Simultaneously, several studies have also indicated negative associations between teenage pregnancy and congenital anomalies [25, 26]. The increased risk of birth defects in younger women possibly result from their unhealthy lifestyle, insufficient ANC or low socioeconomic status. Births in urban areas had higher risks of CHD than those in rural areas, similar to findings in Langfang and Hunan [16, 17]. Women in urban areas may have easy access to high quality ANC, which can lead to a higher detection rate of CHD. Further, environmental exposure and social pressure from urban life should be considered. The inconsistency in relationship between gender and CHD has remained elusive [15, 18, 27]. In most previous studies, prevalence of mild CHD was frequently higher in females than males as reported in Beijing and Germany [19, 27]. The above findings suggest that specific health care services should be strengthened in targeted population.

The increasing incidence of total CHD in our study is consistent with most other studies in China and in other countries [3, 14, 27, 28]. Globally, increasing trends have also been observed in some specific CHD, such as ASD in the USA and SV, ASD, and TOF in Europe [3, 29]. In the study, rising ASD, PDA and VSD should contribute to the substantial increase in overall incidence of CHD. This confirmed previous findings at the global level that the three most frequent subtypes explained 93.4% of rising incidence of total CHD [3]. The increase in incidence of CHD in our study might also reflect a true increase. Moreover, improved CHD screening, prenatal diagnostic technology and follow-up should be taken into account, as explained in Guangdong of China or Europe [14, 29]. In our view, we also could not ignore the influences from changes of maternal characteristics with birth policy shifts. Particularly, women with advanced age increased significantly throughout the period [21].

The total incidence of CHD reached 20.6 per 1000 births in 2018, which is substantially higher than most researches at home and abroad (6–10 per 1000 live births) [3, 14, 18, 28]. However, our rate of CHD is similar to that in southern Israel (24.6/1000 live births), Langfang of China (22.9/1000 live births), but lower than that in Guangxi of China (4.2% pregnancies) [17, 30, 31]. Differences in study population, prenatal detection capability, and ascertainment criteria might explain the heterogeneity of CHD

incidence. In our opinion, the most important reason should be for the variations of criteria. CHD registered by EUROCAT was population based with a long-term follow-up to at least 1 year of life or without age limitations [29]. In Malaysia, they followed up PDA 3 to 6 months of life in term infants and premature infants [28]. In Guangdong, ASD measuring below 5 mm in diameter, fossa ovalis, PDA, or patent foramen ovale were finally confirmed at 6 months after birth, and excluded CHD less than 28 gestational weeks [14]. We conducted a hospital-based study and patients were followed up within 7 days after birth. ASD regardless of diameter and PDA at and over 3 mm in diameter were included. This indicated an overestimation of total CHD in our study. Nevertheless, incidence of CCHD was comparable with data in the National Birth Defects Prevention Network, the International Clearinghouse for Birth Defects Surveillance and Research based on 12 countries (approximately 19.1 per 10000 births) and in Beijing of China (1.46 per 1000 live births) [4, 19, 32].

In the world, the prenatal detection rates varied by regions (13–87%) and CHD subtypes (4.3–100%) [27, 31–36]. In the study, we speculated the primary reason for low detection rates in total CHD and ASD were for the large proportion of ASD and PDA. Another contributing factor was a higher proportion of isolated CHD. As reported, associated CHD was more likely to be detected prenatally than isolated CHD [37]. We noticed similar or even higher prenatal detection rates in some specific CHD than studies in the University of Miami and Denmark, such as double outlet right ventricle, TOF, hypoplastic left heart syndrome, COA, and PTA [33–35]. Limited sample size in per specific CHD might affect stability in some studies. For example, there were only 10 cases with truncus arteriosus in study performed in USA, yielding prenatal detection rate of 70% [35]. The terminated CHD proportion was a slightly higher than study in Denmark (57.8%), but perinatal outcomes was better than isolated CHD in Brisbane, Australia [31, 36]. Comparison of outcomes should noticed the differences in legal requirement for termination and distribution of CHD categories.

There are some limitations for this study. Initially, ASD had the largest proportion in CHD for a relative light standards in the study. Therefore, the observed rates of ASD and CHD in the study might be overestimated than most previous studies [15, 16, 28]. A retrospective case–control study in Sweden including children under 18 years old, showed that only symptomatic ASD were associated adverse outcomes[38]. We should perform further analysis according to the risks of ASD in future. Second, many factors increased risks of CHD. Limited by data in this study, we did not give more analysis involving gene or environmental impacts. Finally, long term follow up is needed considering the accuracy of occurrence and outcomes of CHD.

Abbreviations

Congenital heart disease

CHD

Critical CHD

CCHD

Odds ratio

OR
Confidence interval
CI
Atrial septal defect
ASD
Patent ductus arteriosus
PDA
Ventricular septal defect
VSD
Persistent truncus arteriosus
PTA
Single ventricle
SV
Atrioventricular septal defect
AVSD
Tetralogy of Fallot
TOF
Hypoplastic right heart
HRH
Aortic valve stenosis
AoS
Coarctation of the aorta
COA
Interrupted aortic arch and others
IAA

Declarations

Data Statement

Data were available on reasonable demand contacting with corresponding author.

Acknowledgments

We would like to thank the birth defect surveillance hospitals in Zhejiang province.

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Xiaohui Zhang conceived and supervised the study. Xiaohui Zhang and Yu Sun drafted the manuscript, carried out data collection and do statistical analysis. Jiajun Zhu and Yuning Zhu reviewed the clinical classification of cases and revised the manuscript. LiqianQiu contributed to the design and revised the manuscript. All authors made substantial contributions to the conduct of the study and approved the final manuscript as submitted.

Funding

National Key Research and Development Plan 2018YFC1002702

Ethics approval and consent to participate

The study was approved by the Medical Ethical Committee of Women's Hospital, School of Medicine, Zhejiang University.

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Figures



Figure 1

the incidences of VSD, ASD and PDA over time